applying the buffered solution containing ~~CSF~~ GM-CSF to a chromatographic column, eluting the ~~CSF~~ GM-CSF activity with ~~the~~ a buffered solution containing sodium chloride and collecting the fractions having ~~CSF~~ GM-CSF activity; and

pooling the active fractions, applying the pooled fractions to a C4 reverse phase column and eluting the ~~CSF~~ GM-CSF activity with a 0 to 90% acetonitrile gradient to collect the fractions containing ~~CSF~~ GM-CSF activity;

said GM-CSF being admixed with a pharmaceutically acceptable carrier [according to the process of claim 12].

REMARKS

The application contains claims 1-3, 5-8, 14 and 16, of which claims 1 and 2 are the independent claims. Claims 1-3, 5-8, 14 and 16 have been amended in order to recite the present invention. No new matter has been added.

The Examiner has objected to the title of the invention (paragraph 3 at page 2 of the Office Action) and rejected claims 1, 6, 8, 14 and 16 (paragraph 4 at page 6 of the Office Action) for the reasons stated. In response, these claims have been amended according to the kind suggestions of the Examiner, to comply with the requirements of 35 U.S.C. § 112, second paragraph. The title has also been rewritten to more closely reflect the subject matter of the claims.

The Examiner has rejected claims 1-4, 7-8, 14 and 16 under 35 U.S.C. § 112, first paragraph, since the disclosure allegedly enables only a GM-CSF protein having the sequence shown in Figure 1. Although this rejection is respectfully traversed, solely in order to reduce the issues, Applicants have amended each of their independent claims to recite the "sequence shown in Figure 1," again in conformity with the Examiner's kind suggestions.

The Examiner also contends that claim 7 is not enabled for the reasons stated. In response, this claim has been amended in order to specifically recite the structure variants taught and enabled by the specification.

The final outstanding issue is the Examiner's rejection of the claims as anticipated by Golde et al. (Claims 1-6, 8, 14 and 16), Lusis et al. (Claims 1-6, 8, 14 and 16, and Bleackley et al. or Gough et al. (Claims 1-3, 8, 14 and 16). These rejections are respectfully traversed.

Initially, regarding Golde et al., which the Examiner contends teaches an isolated CSF stimulatory to granulocyte-macrophage colonies, Applicants respectfully wish to point out that it is clear that Golde et al. fails to teach or enable at column 6 the recombinant GM-CSF protein recited in Claim 1. Rather, that disclosure is at best an invitation to experiment. Since Golde fails to teach each and every element of claim 1, this rejection must be withdrawn.

The Examiner also alleges that Golde et al. discloses a protein having the same molecular weight (~30 kDa) as that of the hGM-CSF factor of Claim 2. The Examiner is in error. Golde et al. discloses that CSF has a molecular weight of about 34 kDa (col. 4, line 28). Figure 1 of the present application encodes a protein having a molecular weight of about 18 kDa. When glycosylated, applicant's protein has a molecular weight as great as 26 kDa, far short of the value taught by Golde et al.

Although this feature alone necessarily distinguishes the prior art, Applicants also wish to discuss the Examiner's contention that the specific activity characteristic recited in claim 2 is inherently possessed by Golde et al.'s protein. This contention is, again, in error. The definition of a unit of activity according to Golde et al. (col. 8, lines 38-40), differs fundamentally from that of the present application. Accordingly, Golde et al.'s optimal activity (10 units/mg protein) bears no relationship to applicant's claimed activity, 10^7 units per mg protein.

Finally, the Examiner's statement "the CSF produced by the process described in column 6 of the reference, when used as indicated in column 4 of the reference, would have anticipated the instantly claimed invention" relies on information wholly lacking from the reference, and is merely a speculative conclusion. As such, it appears to be of no relevance. Certainly, in any event, there is no basis in the record for the statement. Accordingly, absent submission of

an Affidavit of the Examiner's personal knowledge in this matter (M.P.E.P. § 2144.03), this is an improper basis for rejecting the claims.

The Examiner states that Lusis et al. teaches production of granulocytes and macrophages by contact with GM-CSF protein produced as a translation product of Mo cell RNA. Nonetheless, Lusis et al. fails to anticipate for the same reasons as Golde et al., e.g., Lusis et al. fails to teach every element of the claimed invention.

Lusis et al. does not teach a recombinant GM-CSF, but merely provide an invitation to experiment. The alleged inherent molecular weight of Lusis et al. (ca. 44 kDa for the unglycosylated protein) differs greatly from the instant protein having a sequence of Fig. 1 (ca. 18 kDa). Although Lusis et al. provides no sequence information to confirm the Examiner's presumption that Lusis et al.'s protein has the same amino acid sequence shown in Fig. 1, the molecular weight taught by Lusis et al. clearly establishes that it does <u>not</u>. Nor does the bioactivity reported by Lusis et al. have any relation to that expected for a purified isolated GM-CSF protein. In fact, the language cited on page 77 not only fails to show anticipation, but actually teaches away from applicants' invention. Lusis et al.'s <u>in vitro</u> translation has not been successfully applied by Applicants or others, including Lusis et al., in obtaining a recombinant GM-CSF protein having the sequence of Fig. 1.

The Examiner's last rejection over Bleackley et al. and Gough et al., each of which allegedly teaches production of GM-CSF. Applicants respectfully traverse this rejection, since neither teaches every element of the claimed invention.

The Examiner concedes that both references are limited to murine CSF. Applicants' claimed invention is, in the pending claims, directed to human GM-CSF protein. As is well-understood in the art, there is very limited homology between murine GM-CSF and human GM-CSF. Accordingly, disclosure of murine GM-CSF is neither anticipatory of, nor renders obvious, the claimed invention.

In view of the foregoing amendment and remarks, Applicants respectfully requests favorable reconsideration and early allowance of the present application.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 758-2400. All correspondence should be directed to our below listed address.

Respectfully submitted,

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